Resection of vestibular schwannomas after stereotactic radiosurgery: a systematic review

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OBJECTIVE Multiple short series have evaluated the efficacy of salvage microsurgery (MS) after stereotactic radiosurgery (SRS) for treatment of vestibular schwannomas (VSs); however, there is a lack of a large volume of patient data available for interpretation and clinical adaptation. The goal of this study was to provide a comprehensive review of tumor characteristics, management, and surgical outcomes of salvage of MS after SRS for VS.

METHODS The Medline/PubMed, Scopus, CINAHL, Cochrane Library, and Google Scholar databases were queried according to PRISMA guidelines. All English-language and translated publications were included. Studies lacking adequate study characteristics and outcomes were excluded. Cases involving neurofibromatosis type 2, previous MS, or malignant transformation were excluded when possible.

RESULTS Twenty studies containing 297 cases met inclusion criteria. Three additional cases from Rush University Medical Center were added for 300 total cases. Tumor growth with or without symptoms was the primary indication for salvage surgery (92.3% of cases), followed by worsening of symptoms without growth (4.6%) and cystic enlargement (3.1%). The average time to MS after SRS was 39.4 months. The average size and volume of tumor at surgery were 2.44 cm and 5.92 cm³, respectively. The surgical approach was retrosigmoid (42.8%) and translabyrinthine (57.2%); 59.5% of patients had a House-Brackmann (HB) grade of I or II. The facial nerve was preserved in 91.5% of cases. Facial nerve preservation and HB grades were lower for the translabyrinthine versus retrosigmoid approach (p = 0.31 and p = 0.18, respectively); however, fewer complications were noted in the translabyrinthine approach (p = 0.29). Gross-total resection (GTR) was completed in 55.7% of surgeries. Studies that predominantly used subtotal resection (STR) were associated with a lower rate of facial nerve injury (5.3% vs 11.3%, p = 0.07) and higher rate of HB grade I or II (72.9% vs 48.0%, p = 0.00003) versus those using predominantly GTR. However, majority STR was associated with a recurrence rate of 3.6% as compared to 1.4% for majority GTR (p = 0.29).

CONCLUSIONS This study showed that the leading cause of MS after SRS was tumor growth at an average of 39.4 months after radiation. There were no significant differences in outcomes of facial nerve preservation, postoperative HB grade, or complication rate based on surgical approach. Patients who underwent STR showed statistically significant better HB outcomes compared with GTR. MS after SRS was considered by most authors to be more difficult than primary MS. These data support the notion that the surgical goals of salvage surgery are debulking of tumor mass, decreasing compression of the brainstem, and not necessarily pursuing GTR.

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KEYWORDS acoustic neuroma; microsurgery; salvage surgery; vestibular schwannoma; oncology; stereotactic radiosurgery

Vestibular schwannomas (VSs) are typically benign tumors arising most commonly from the nerve sheath of the superior division of cranial nerve VIII. The incidence, as determined by modern population-based studies, is between 1.1 and 4.2 per 100,000 people.¹-⁶ The majority of tumors are unilateral and sporadic; however, bilateral tumors are seen in association with neurofibromatosis type 2 (NF2).⁷

Treatment options for VS may be divided into three main groups: conservative management, microsurgery (MS), and stereotactic radiosurgery (SRS). Historically, MS was the predominant treatment of choice. Neverthe-
less, the incremental experience and long-term follow-up with fractionated stereotactic radiotherapy (fSRT) and SRS led to their increased use as an adjunct to surgery or as the primary treatment modality for VS in the past decades. There is a growing body of literature on SRS as the primary treatment of VS. Tumor control rates are generally good for fSRT and SRS, ranging from 81% to 100% at 5 years.8–10 Along with the increased use of SRS as a primary treatment for VS, broader indications, imperfect control, and an aging patient population have led to an increase in the number of patients requiring MS after failed primary SRS.11

Despite the robust literature on primary SRS for VS, there is a relative paucity of studies addressing patients who experience treatment failure. The goal of this systematic review is to synthesize the outcomes of previously published literature and add our experience on patients with VS requiring salvage surgery after failed SRS.

Methods

The review protocol was conducted in accordance with PRISMA guidelines. Five online databases (Medline/PubMed, Scopus, CINAHL, Cochrane Library and Google Scholar) were systematically searched by two independent reviewers using filters for English-language articles, publication between 1990 and 2019, and the following search string: ((“Neuroma, Acoustic”[Mesh] or (vestibular and (schwannoma or schwannomas)) or “acoustic neuroma”)) AND (“Radiosurgery”[Mesh] or radiosurgery OR radiosurgical or SRS or “cyberknife” or “gamma knife” or radiotherapy or X-knife or Novalis or “stereotactic radiation treatment”)) AND (“Microsurgery”[Mesh] or microsurgery or surgery OR surgical or resection).

Titles and abstracts were screened by the first author for surgery that occurred following irradiation of VSs. The remaining articles were then reviewed by the first author based on the criteria outlined below and reviewed by the second or third authors. Cases were also added from the authors’ institution and categorized as “Rush data” in the review.

Inclusion Criteria

Full articles in which at least 1 patient underwent primary fSRT or SRS for a VS that required subsequent salvage MS were included. Studies needed to have at least 3 of the following variables in regard to tumor characteristics: type of radiation treatment, radiation treatment dose, surgery indication, time interval between SRS and MS, and tumor size; and at least 3 of the following variables in regard to surgical outcome: approach, resection success, tumor control, facial nerve preservation, preoperative House-Brackmann (HB) grade, postoperative HB grade, and complications.

Exclusion Criteria

To aid in having a homogenous patient population, cases of malignant transformation of VS following SRS, patients with NF2, or those with previous MS were excluded from our analysis. In instances in which the data reported were pooled, the study and patient populations were included in the review if the sum of patients that fell into these categories did not make up more than 50% of the patient population.

Data Extraction

Data was extracted by the first author and verified by the second or third authors. Variables included number of participants, average age, sex, laterality, previous surgery, NF2, malignancy, follow-up duration, SRS method, SRS dose, indications for surgery, time between SRS and MS, tumor size/volume, MS approach, extent of resection, tumor control, facial nerve preservation, preoperative HB grade, postoperative HB grade, postoperative hearing, difficulty with dissection, complications, and additional notes.

Data Processing

Potential bias in the studies was not assessed when compiling and processing variables. All variables collected were summed and averaged based on the number of patients in each study. In the comparison between surgical approaches, a 2-sided t-test was used for significance. In the comparison between extent of resection, a 1-sided t-test was used. Analysis was overseen by a statistician.

Results

The initial query of databases yielded 1738 articles (Fig. 1). The title and abstract of the 1131 results were screened by two reviewers for any type of surgery that occurred following SRS treatment of VS. After screening, 236 articles were reviewed in full to determine eligibility based on the inclusion and exclusion criteria. One hundred eighty-six of these studies reported the tumor control rate following SRS but provided no further details on the subsequent salvage surgery in the full text. A further 19 papers related to malignant transformations of VS following SRS were excluded. Three studies that evaluated only MS following primary treatment of VS with a combination of surgery and SRS were excluded. Five studies that met all other criteria were excluded because all their patients were used in a later paper, which was included in the review. Three studies that passed the title and abstract review were not included because an English translation of the full study could not be obtained.

Ultimately, 20 studies met all inclusion and exclusion criteria for this review. Data compiled from the Rush University Vestibular Schwannoma database were added to the total results to bring the total number of studies to 21.

Patient and Radiation Characteristics

The 21 studies reviewed included 300 patients who required MS following failed SRS for treatment of a VS. The average age at the time of surgical salvage was 53.2 years. Females made up 63.9% of the total population and 60.7% of the tumors were right-sided (Table 1).

Individual cases of prior MS, NF2, or malignant transformation are included in the pooled data, as these cases could not be parsed from the aggregate data of their respective studies. Three of the 21 studies included at least 1
case from one of these categories. Patients falling into the categories of prior MS, NF2, or malignant transformation represent just 5.0%, 6.9%, and 0.7%, respectively, of the total population analyzed.

The average tumor size at the time of surgery was 2.44 cm and the average volume was 5.92 cm$^3$ (Table 1). Gamma Knife surgery (GKS; Elekta) was the most frequent type of SRS (n = 218) that required surgical salvage in the studies listed, followed by linear accelerator (LINAC; n = 30), fSRT (n = 23), and CyberKnife (CK; Accuray; n = 10). The weighted average doses of the SRS treatments were 12.7 Gy (GK), 27.1 Gy (LINAC), 31.5 Gy (fSRT), and 21.5 Gy (CK).

**Surgical Indication and Management**

Tumor growth, with or without symptoms, comprised 92.3% of the indications for surgery following failed SRS; 4.6% of surgeries occurred following a worsening of symptoms (i.e., neurological deterioration, unbearable facial pain, or trigeminal neuralgia) after SRS despite no tumor growth. Additionally, 3.1% of surgeries occurred due to cystic enlargement of the tumor (Table 1).

The surgical approaches used for salvage MS of VS after failed SRS were retrosigmoid approaches and translabyrinthine approaches, representing 42.8% and 57.2% of surgeries, respectively. According to the authors, 68.5% of salvage surgeries were described as more difficult than a primary MS for VS (Table 2).

**Surgical Outcomes and Complications**

Facial nerve anatomical preservation was 91.5% in studies that reported this outcome. The average postoperative HB grade among all studies was 2.58, with 59.5% of patients having an HB grade of I or II (Table 2).

The facial nerve preservation rates and postoperative HB grades were broken down by surgical approach—retrosigmoid or translabyrinthine—in studies that provided the data separately. For retrosigmoid approach surgeries, the facial nerve preservation rate was 89.7% and 61.0% of patients had an HB grade of I or II. For translabyrinthine approaches, the facial nerve preservation rate was 87.8% and 51.0% of patients had an HB grade of I or II. Nine complications were noted in the 68 retrosigmoid cases, while there were 8 complications in the 98 translabyrinthine cases.

There were 10 reported CSF leaks as a result of salvage MS, for a total rate of 3.3%. Other surgical complications included 3 patients with meningitis, 3 pseudomeningoceles, 2 cerebral strokes, 2 incidences of cerebellar edema, 2 cases of syndrome of inappropriate antidiuretic hormone...
884 J Neurosurg Volume 135 • September 2021

TABLE 1. Included studies, demographics, tumor characteristics, and indications for surgery

<table>
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<tr>
<th>Authors &amp; Year</th>
<th>No. of Pts</th>
<th>Age (yrs)</th>
<th>Females (%)</th>
<th>Rt-Sided</th>
<th>Mean Tumor Size (cm)</th>
<th>Mean Tumor Volume (cm³)</th>
<th>Mean Duration Btwn SRS and MS (mos)</th>
<th>No. w/ Tumor Growth</th>
<th>No. w/ Growth &amp; Symptoms</th>
<th>No. w/ Symptoms Alone</th>
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<tr>
<td>Total/average</td>
<td>300</td>
<td>53.2</td>
<td>168 (63.9)</td>
<td>37</td>
<td>60.7%</td>
<td>2.44</td>
<td>5.92</td>
<td>39.4</td>
<td>140 (71.4%)</td>
<td>41 (20.9%)</td>
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</table>

NA = not available; Pts = patients.

secretions, 2 transient vocal cord paralyses, 1 brainstem stroke, 1 hemiparesis, 1 hematoma, 1 venous thrombosis, 1 dehiscence, 1 wound infection, 1 persistent headache, 1 pneumocephalus, and 1 epileptic seizure.

Gross-total resection (GTR) was achieved in 55.7% of patients, compared with 44.3% of subtotal resection (STR; n = 291 total GTR or STR cases). Studies in which a majority of patients underwent STR had a lower rate of facial nerve severance than those where the majority of patients underwent GTR: 5.3% versus 11.3%, respectively (p = 0.07). Postoperative HB grade I/II was 72.9% for STR versus 48.0% for GTR (p = 0.00003). While more studies are needed directly comparing STR and GTR, preferably with institutional and patient controls, these data show that among published studies, using primarily STR led to better facial nerve outcomes.

Discussion

Patient and Radiation Characteristics

The average tumor size at the time of surgery was 2.44 cm and the average volume was 5.92 cm³. This average tumor size would classify as a grade 3 House and Koos score, indicating a moderately large tumor. All studies with a moderate or large sample size (> 5 patients) had an average tumor size of at least 2 cm or average volume of at least 4.67 cm³, with the notable exception of Aboukaïs et al., who reported an average tumor volume of just 1.84 cm³ at the time of surgery. Because tumor growth was the major indicator for surgical salvage, it is unsurprising that the average tumor in most studies was moderately large.

Regarding SRS treatment, GKS was the most frequent SRS modality that required surgical salvage in the studies listed. This is likely due to GKS historically being the most frequently used modality for SRS for primary VS. No study mentioned any differences in surgical techniques or outcomes based on SRS treatment type. Radiation doses for treatment of VS have been continually decreasing in recent years; the impact this will have on salvage surgery following radiation is unknown. Adverse radiation effects may decrease, but tumor control rates from primary SRS may fall with decreasing doses, leading to a greater incidence of recurrent VS. Schumacher et al. report that despite SRS doses decreasing from a median of 16 Gy in older studies to 12.5 Gy in newer studies, there are similar reported rates of tumor control. Within our study, we were unable to investigate the superiority of tumor control for individual types of SRS, consistent with the published literature.

Surgical Indication and Management

The International Stereotactic Radiosurgery Society pub-
lished consensus practice guidelines on the management of VS with respect to SRS. While this guides physicians in primary diagnosis of VS, there is less literature regarding the management of VS after failed SRS. Continued growth of the VS is the leading indication for the requirement of MS (>90% of salvage surgeries) in our review. The other indications for salvage surgery listed by authors were worsening of symptoms (i.e., neurological deterioration, unbearable facial pain, and trigeminal neuralgia) and cystic enlargement.

Transient expansion occurs in the majority of VSs treated with SRS. Nagano et al. found that 74% of VSs treated with GKS had a volume increase of at least 10%, with the average tumor expanding 47% at its peak. The mean time to shrink back to the original size prior to SRS was 12 months. Due to these transient expansions, adverse radiation effects occur most commonly between 6 and 18 months and self-resolve in more than half of cases within 3–6 months. Furthermore, the cranial nerves and brainstem are most susceptible to surgical injury during this time. Nonaka et al. advocate for a 3-year minimum waiting period between SRS and surgical salvage, barring the development of severe symptoms.

Most studies in our review avoided surgery during the transient period as the average duration between SRS and MS was 39.4 months among all studies. However, there are quite a few exceptions to this general recommendation in the literature, often due to severe symptomatic progression from tumor expansion. Barring exceptions as previously mentioned, our institutional preference is to avoid surgical intervention during the period of transient expansion, with judicious use of steroids as necessary.

Most recurrent VSs grow at a steady rate following SRS; however, Nonaka et al. reported that 10% of the tumors they treated with salvage MS were quiescent for many years prior to rapid growth. Iwai et al. speculate that this may be due to malignant transformation from radiation injury. An additional complication that can arise is cystic expansion. Shuto and Matsunaga present 2 cases of symptomatic cyst formation occurring 4 and 12 years following GKS treatment for noncystic VS. They speculate that this may be due to repeated minor hemorrhages or the extravasation of fluid from the lesion. Thus, many authors call for SRS studies with longer follow-up times to better determine the rate of delayed radiation injury or tumor control failure. It must be stated that publications have advocated for the use of repeat SRS in instances of persistent growth of VSs after initial SRS. Kano et al. published a study on a small series of 6 patients who received repeat SRS to the same tumor for progressive growth at a median of 63 months after initial treatment. In all of these patients, tumor control was obtained at a median 29 months of follow-up. Thus, while our review does not address this method of treatment, it is a viable option to be considered for patients who may be considered at high risk for surgical intervention. Our institutional preference in patients with persistent growth after surgery during these periods. Nonaka et al. advocate for a 3-year minimum waiting period between SRS and surgical salvage, barring the development of severe symptoms.

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SRS would be surgical intervention, as it provides critical debulking of mass effect and, in our experience, superior tumor control and clinical outcome.

Retrosigmoid and translabyrinthine approaches were utilized nearly equally across all studies (42.8% vs 57.2%, respectively; n = 250). The translabyrinthine approach is often cited as providing the best exposure of the cerebellopontine angle for VS removal. The surgery does not spare hearing, but the vast majority of patients requiring salvage surgery following failed SRS have little to no hearing. Limb et al. preferred using a retrosigmoid approach as it allowed them to have early exposure to the cranial nerves within the internal auditory canal.24

In our analysis comparing studies that used only a retrosigmoid or translabyrinthine approach (n = 166), the retrosigmoid approach led to higher rates of facial nerve anatomical preservation (89.7% vs 87.8% for translabyrinthine, p = 0.31) and lower postoperative HB scores (61.0% vs 50.6% HB grade I/II for translabyrinthine, p = 0.18). However, there were lower complication rates listed for surgeries performed via the translabyrinthine approach: 8.2% for translabyrinthine and 13.2% for retrosigmoid (p = 0.29). Overall, there is not a strong indication for using one approach over the other in salvage MS for VSs treated with primary SRS. We advocate for the proper surgery for the proper patient in this scenario, prioritizing surgeon comfort with an approach.

Difficulty in dissection is a subjective variable, and there appear to be differences in how different authors classify dissections as difficult. For the sake of comparison, tumors were counted as being difficult dissections if the authors mentioned the surgery or dissection as being more difficult than average. By these criteria, 68.5% of classified tumors were rated as more difficult than normal. Tumors could be more difficult to resect for several reasons. The most frequently cited reasons were adhesion to cranial nerves and lack of a facial plane.17,24 As a consequence of greater adhesion between the tumor and the cranial nerves following SRS, STR is often performed out of necessity or by surgeon choice. GTR was completed on 55.7% of the surgeries that reported extent of resection (n = 291), with the rest of the surgeries leaving at least some residual tumor. For primary MS for VS, the GTR rate is much higher at 81.6%.6 The decision of whether to aim for GTR or plan for STR is a significant debate in the literature reviewed.

Friedman et al. achieved GTR in 78.9% of MSs following SRS prior to 2005.16 After 2005, GTR in their series decreased to 56.5% of cases following a switch to a more conservative approach in the hope of improving facial nerve outcomes. The results of the change have been promising early on, as 86% of patients since 2005 have had HB grade I or II 1 year postoperatively. Furthermore, among all patients who had a preoperative HB grade of I or II, the rate of postoperative HB grade I/II was 42.9% for GTR (n = 42) and 84.6% for STR (n = 13). Given these results, they advocate for planned STR in these patients, although they caution that there are still limited data on recurrence rates for residual tumors.

In contrast, Gerganov et al. continue to recommend GTR, as the follow-up periods of authors who advocate for STR is too short (up to 36 months) to make conclusions about its efficacy.17 Additionally, a tumor that is resistant to SRS treatment may carry even greater growth potential than a residual tumor left from primary MS, and therefore recurrence rates after primary STR MS may underestimate the rate for these tumors. Husseini et al. similarly recommend attempting GTR in all cases, except cases of elderly patients or those with cystic tumor when the cyst wall is in contact with vital structures.19

Wise et al. evaluated the potential of GTR on a case-by-case basis. They aimed to achieve GTR in all cases, but were quick to change to STR based on both intraoperative impression and electroprognostic testing. The GTR rate from their study was 49%.30

Our analysis included a breakdown of studies by GTR versus STR, when reported (n = 291). Studies in which the results between GTR and STR could not be separated were placed into whichever category a majority of the cases were. The biggest difference between the GTR and STR populations was the difference in the proportion of patients who had postoperative HB grade I/II: 72.9% for STR versus 48.0% for GTR (p < 0.05). While more studies are needed directly comparing STR to GTR, preferably with institutional and patient controls, these data show that among published studies, using primarily STR led to better facial nerve outcomes.

Additional intervention following salvage surgery, be it radiation or further surgery, was low in both groups. The tumor control rate was 98.6% for the GTR group versus 96.3% for STR. The overall occurrence of tumor regrowth was low in each population (5 total recurrences), and this was not statistically significant (p = 0.29). Additionally, there was a wide variety in reported follow-up times. At this point, it appears that STR does lead to higher recurrence rates, but the true rate and effect of this is unknown because of the low rate of occurrence and variability in follow-up. A summary of results based on surgical approach and extent of tumor resection is shown in Fig. 2.

Surgical Outcomes and Complications

The facial nerve anatomical preservation rate for MS following primary SRS was 91.5%. This is lower than the preservation rate of 95% for primary MS.3,33 Just 59.5% of patients in this review had an HB grade of I or II in the postoperative period. Across 30 studies of primary MS for VS, the rate of postoperative HB grade I or II was between 55.8% and 98.6%.34 The lower rates of facial nerve preservation and HB grade I or II bolster the opinion of many authors that surgery is more difficult in tumors that have previously been irradiated.

Among studies with at least 10 participants, an HB grade of I or II was achieved in more than 70% of cases by Breshears et al.,14 Iwai et al.,20 Nonaka et al.,11 and Wise et al.30 Breshears et al. reported their HB grades at 14 months postoperatively, whereas most other studies recorded postoperative HB grades in the first week following surgery. It is also worth noting that Iwai, Nonaka, and Wise all used STR on more than half of their Ms, which may have aided in better than average postoperative HB grades.

A total of 34 complications were noted among the 300 cases (11.3%). The most common complication was CSF leak, which occurred in 3.3% of cases. The total complication rate as well as the CSF leak rate are higher than would be
expected from primary VS MS. A large study across multiple institutions of primary MS patients without NF2 showed a total complication rate of 5.3%, with a CSF leak rate of 2.03%. The next leading complications noted in this primary MS study were dysphagia, CSF leak, urinary tract infection, intracerebral hemorrhage, vocal cord paralysis, and subdural hematoma. The translabyrinthine approach was found to be a contributing factor to an increased risk of CSF leak in primary VS MS, along with longer operative time.

It is our practice to pursue the maximal safe resection. This typically translates to a near-total or subtotal resection, with the goal of anatomical preservation of the facial nerve, and close observation in the postoperative period with continual assessment for further SRS for life. A representative case is shown in Fig. 3.

There are several limitations to this study. The retrospective nature of the work made it difficult to fully analyze data in the studies included. Due to the pooled data report of many studies, comparing cause and effect between variables such as resection amount and tumor control rate was challenging. With raw data from each of these studies, stronger conclusions could be made about the efficacy of approach types and extents of resection.

Conclusions

Microsurgery following SRS for VSs has proved to be more difficult than primary surgery. Our study shows lower rates of GTR, facial nerve preservation, and good

**FIG. 2.** Comparison of surgical approach and extent of resection in salvage surgery.

**FIG. 3.** Axial MR images obtained in a 60-year-old man with a history of a 2.2-cm right VS who underwent GKS therapy 4 years prior to presentation (A). Two years following GKS, a decrease in tumor size (to 1.9 cm) was noted (B). Four years following GKS, serial imaging showed the tumor size began to increase (2.6 cm; C) and the patient developed a severe sensorineural hearing loss of the right ear. The patient underwent a right translabyrinthine approach for STR of the lesion with full anatomical preservation of cranial nerve VII. Postoperatively, his facial nerve function was normal. MRI was obtained 6 months following surgery (D).
outcomes (defined as HB grade I or II) in this population of patients. In the case of salvage surgery, we conclude that a conservative approach to resection with an emphasis on brainstem decompression and cranial nerve preservation over a GTR is preferred for an optimal clinical outcome.

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References


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**Supplemental Information**

**Previous Presentations**
Parts of this study were presented as an abstract at the North American Skull Base Society annual meeting, February 9, 2020, as “Surgical resection after radiosurgery for the management of vestibular schwannomas: a systematic review.” The abstract was published by the *Journal of Neurological Surgery: Skull Base* in February 2020.

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